REMARKS

I. Status of the Claims

Claims 66-88 are pending and under consideration. With this Amendment, Claims 66-88 are cancelled and new Claims 89-103 are added. Thus, after entry of this Amendment, Claims 89-103 are pending and under consideration.

Support for new Claims 89 and 92-94 can be found, for example, in cancelled Claims 66 and 82 and in paragraph 89 of the specification as originally filed, Example 1 (paragraphs 237-239 in the specification as originally filed), and Example 3 (paragraphs 242-244 in the specification as originally filed). Support for new Claims 90-91 can be found, for example, in cancelled claims 66, 69, 84 and in paragraph 126 of the specification as originally filed. Support for new Claim 95 can be found, for example, in paragraphs 57 and 212 in the specification as originally filed. Support for new Claim 96 can be found, for example, in paragraphs 9 and 20 of the originally filed specification. Support for new Claim 97 can be found, for example, in paragraph 31 of the originally filed specification. Support for new Claim 98 can be found, for example, in cancelled Claims 72 and 76. Support for new Claim 99 can be found, for example in cancelled claims 74 and 77. Support for Claim 100 can be found, for example, in cancelled Claims 75 and 80. Support for Claim 101 can be found, for example, in cancelled Claim 73. Support for Claim 102 can be found, for example, in cancelled Claim 78. Support for Claim 102 can be found, for example, in cancelled Claim 70.

New independent Claim 89 recites many of the elements of cancelled claim 66, including a first and second integration cassette comprising, respectively, a first and second exchangeable reporter segment, and a first and second target cassette comprising,

respectively, a first and second scorable homeostatic reporter element. Cancelled claim 66 recited at least one rec element encoding FLP recombinase activity recognizing the frt recombinase recognition sites of a and b, and a FLP recombinase capable of recognizing the frt recombinase recognition sites of d and e, whereas new claim 89 recites at least one rec element encoding FLP recombinase activity recognizing the frt recombinase recognition sites of a, b, c, and d.

Additional elements in Claim 89, not recited in claim 66, are a first subunit of a multisubunit complex and a second subunit of the multisubunit complex. Support for these elements can be found in paragraphs 207-213 and claim 17 of the specification as originally filed. No new matter has been added by virtue of the amendments.

II. Rejection under 35 U.S.C. §112, second paragraph

Claims 85-88 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claims 85-88 are cancelled, rendering the objection moot.

III. Rejection under 35 U.S.C. §103(a)

The Patent Office has made the following rejections under 35 U.S.C. § 103(a):

Claims 66 and 69-88 are rejected as being unpatentable over Cheo *et al.*, U.S. Patent Application Publication No. 2002/0007051 ("Cheo *et al.*") in view of Seibler *et al.*, 1997, Biochemistry, 36:1740-1747 ("Seibler *et al.*") and Mazda *et al.*, 1994, Journal of Immunological Methods, Vol. 169, pages 53-61, 1994 ("Mazda *et al.*").

Claims 66-88 are rejected as being unpatentable over Cheo *et al.*, U.S. Patent Application Publication No. 2002/0007051 ("Cheo *et al*") in view of Seibler *et al.*, 1997,

Biochemistry, 36:1740-1747 ("Seibler *et al.*"), Ow, U.S. Patent Application Publication No. 2002/0123145 ("Ow"), and Mazda *et al.*, 1994, Journal of Immunological Methods, Vol. 169, pages 53-61 ("Mazda *et al.*").

The rejections are moot as applied to cancelled Claims 66-88. Applicant traverses the rejections as they apply to new Claims 89-103.

A. Criteria for Establishing a Prima Facie Case of Obviousness

To establish a proper prima facie case, three criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation that the modification or combination would be successful. Finally, the prior art reference (or references when combined) must teach all the limitations of the rejected claims. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based upon Applicant's disclosure. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991), citing In re Dow, 5 USPQ2d 1529 (Fed. Cir. 1988); MPEP § 2142.

B. The combination of Cheo *et al.*, Seibler *et al.*, and Mazda *et al.*, fails to teach or suggest all of the limitations recited in amended Claim 89.

Claims 66 and 69-88 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Cheo *et al.* in view of Seibler *et al.* and Mazda *et al.* Claim 66 has been cancelled. New Claim 89 recites, among other things, a cellular expression system comprising a first integration cassette and a second integration cassette that are capable of stable and

random insertion into first and second discrete genomic positions, respectively, in a host cell. Claim 89 further recites a first target cassette comprising a nucleic acid encoding a first subunit of a multisubunit complex and a second target cassette comprising a nucleic acid encoding a second subunit of the multisubunit complex.

As recited in Claim 89, upon introduction of a rec element, the first target element is capable of undergoing site-specific exchange with the first exchangeable reporter segment in a first discrete genomic position and the second target cassette is capable of undergoing site-specific exchange with the second exchangeable reporter segment located in a second discrete genomic position.

The expression system as claimed by the Applicant allows for the selection of a recombinant host cell that expresses two scorable reporter genes located at two discrete genomic locations at high and equivalent levels. Subsequent introduction, into the recombinant host cell, of two target cassettes comprising two subunits of a multisubunit complex allows for the generation of a recombinant host cell that expresses the two subunits at high and equivalent, or equimolar, levels. This facilitates efficient expression of a properly folded multisubunit protein such as an antibody comprising 2 heavy and 2 light chains.

Cheo *et al.* teach materials and methods for joining or combining, two or more segments or molecules of nucleic acid by the recombination reaction between recombination sites (Paragraph 0043). Furthermore, Cheo et al. teach methods of recombination between segments of nucleic acids in one or more episomal vectors. Cheo et al. do not teach site specific recombination between an exchangeable reporter segment located in a discrete genomic location and a target cassette located in an episomal vector.

Because Cheo *et al.* teach multiple target cassettes that undergo site-specific recombination prior to any integration into the host cell genomic DNA, use of the system taught by Cheo *et al.* to express recombinant proteins from constructs that have been integrated into the host cell genome necessitates that nucleic acids encoding individual subunits of a multisubunit protein be located within the same genomic integration site. This is different from the Applicant's claimed invention in which nucleic acids encoding individual subunits will be located in separate or discrete genomic positions, thus allowing independent regulation of transcription. Furthermore, the Applicant's invention as claimed allows selection of recombinant host cells that will express high and equivalent levels of the two subunits. Expression of two subunits within a single construct as taught by Cheo et al. often results in non-equivalent levels of expression of the two subunits.

Seibler *et al.* do not teach an expression system to express multisubunit proteins. Furthermore, Seibler *et al.* do not teach nucleic acids encoding individual subunits to be site-specifically recombined into separate or discrete genomic positions within a single recombinant host cell. Thus, Seibler *et al.* do not cure the deficiency of Cheo *et al.*

The Patent Office cited Mazda *et al.*, as teaching nucleic acid constructs comprising the murine CD8α gene cDNA. Claims 66 and 69-88 have been cancelled and new Claim 89 does not recite CD8. Furthermore, Mazda *et al.* do not teach an expression system in which nucleic acids encoding individual subunits will be located in separate or discrete genomic positions. Thus, Mazda *et al.* do not cure the deficiency of Cheo *et al.*

At a minimum, the combination of Cheo *et al.*, Seibler *et al.*, and Mazda *et al.* fails to teach or suggest all of the limitations recited in new Claim 89. Specifically, the

combination of Cheo *et al.*, Seibler *et al.*, and Mazda *et al.* fails to teach or suggest site-specific recombination of two nucleic acid sequences encoding two subunits of a multi-subunit protein into two discrete and separate genomic positions. Applicant respectfully submits that the new Claim 89 is patentable over Cheo *et al.*, in view of Seibler *et al.* and Mazda *et al.*

C. The combination of Cheo *et al.*, Seibler *et al.*, Ow and Mazda *et al.*, fails to teach or suggest all of the limitations recited in amended Claim 89.

Amended Claim 89 has been summarized above.

The teachings of Cheo *et al.*, Seibler *et al.*, and Mazda *et al.* have been discussed above.

The Patent Office states that Ow teaches, among other things, that the rec element can be included in the first integration cassette and that the rec element can be included in the first target cassette. Ow does not to teach or suggest site-specific recombination of two nucleic acid sequences encoding two subunits of a multi-subunit protein into two discrete and separate genomic positions. Applicant respectfully submits that the new Claim 89 is patentable over Cheo *et al.*, in view of Seibler *et al.* Ow, and Mazda *et al.*

Claims 90-103 depend from independent Claim 89 and therefore include all the limitations of Claim 89. Thus, the arguments as presented above with regard to Claim 89 are also applicable to dependent Claims 90-103.

CONCLUSION

In view of the foregoing, the Applicant believes all claims now pending in this application are in condition for allowance and an action to that end is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 510-284-8905.

Respectfully submitted,

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